REMARKS

Claims 1-28 are pending in this application.

Claims 24 and 28 have been amended to specify that the patch is a hydrogel patch. Support for this amendment may be found at page 10, lines 1-5.

As no new matter is added, the Applicants respectfully request the entry of the amendments.

Applicant respectfully requests reconsideration of the application in view of the remarks made herein.

REJECTION UNDER 35 U.S.C. §112

Claims 1-5 and 19-27 have been rejected under 35 U.S.C. §112, second paragraph. The Examiner asserts that it is unclear what is meant by the phrase "at least ameliorating a symptom associated with".

The law is clear that "[i]f the claims, read in the light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." North American Vaccine, Inc. v. American Cyanamid Co. 28 USPQ 2d 1333, 1339 (Fed. Cir. 1993), cert. denied, 114 S. Ct. 1645 (1994).

The Applicant submit that the claims, read in the light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and in particular the meaning of the phrase "at least ameliorating a symptom associated with".

The meaning of the phrase "at least ameliorating a symptom associated with" is clearly defined in the specification. The phrase "at least an amelioration" is specifically defined in the specification at page 7, lines 8-9:

> By "at least an amelioration" is meant at least a reduction in the magnitude of the symptom, including a complete cessation or removal of the symptom.

Furthermore, immediately thereafter the above-noted definition of "at least an amelioration", symptoms ameliorated by the subject methods are clearly described (page 7, lines 10-15):

> Symptoms ameliorated by the subject methods include one or more of: (a) weakness in at least one hand; (b) numbness or tingling in the thumb and next 2 or 3 fingers of 1 or both hands; (c) numbness or tingling of the palm of the hand joint pain (wrist pain) in 1 or both hands; (d)impaired fine finger movements in 1 or both hands; (e) weak grip; (f) difficulty bringing the thumb across the palm to meet the other fingers (thumb opposition); (g) pain in the wrist and hand; and the like.

Accordingly, the meaning of the phrase "at least an amelioration" is clearly provided, as well as symptoms associated with carpal tunnel syndrome that may be ameliorated by the subject methods. As such, the meaning of the phrase "at least ameliorating a symptom associated with" is clearly provided in the specification and as such the claims, read in the light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention and in particular the meaning of the phrase "at least ameliorating a symptom associated with".

For at least the reasons described above, the Applicant respectfully request this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. §103

Claims 1-18 and 24-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Petrus (U.S. 6,399,093 B1) in view of Bichman et al (U.S. Patent No. 5,980,921). The Applicants respectfully submit that Claims 1-18 and 24-28 are patentable over the cited references.

Independent Claims 1, 6, 11, 24 and 28, and the claims that depend therefrom, specify the application of an effective amount of a topical NSAID formulation to a location proximal to the carpal tunnel/median nerve. For example, Claim 1 specifies that the topical formulation is applied to a palmer dermal surface proximal to the carpal tunnel to at least ameliorate a symptom associated with carpal tunnel syndrome (CTS); Claims 6 and 28 specify that the topical

formulation is applied to a palmar dermis; Claim 11 specifies that the topical formulation is applied to the palmar dermis proximal to the median nerve; and Claim 24 specifies that the topical formulation is applied to the palmar dermis proximal to the carpal tunnel to at least ameliorate a symptom associate with pressure applied to the median nerve.

The Petrus patent merely teaches a method and composition for the treatment of musculoskeletal disorders by application of a topical composition. However, the only mention of carpal tunnel syndrome (CTS) in Petrus is a notation in the background section that describes that occupational injury may result in musculoskeletal injuries and notes CTS as an occupational hazard (abstract, col. 1, lines 27-43). Petrus does not teach or suggest the effective treatment of CTS or median nerve pressure by application of a topical formulation, NSAID-containing or otherwise, to an area proximal the carpal tunnel. In fact, Petrus fails to specifically teach the application of an NSAID formulation to an area about the carpal tunnel/median nerve to treat any condition at all. While Petrus describes that a component of the inventive composition may include NSAIDs (col. 4), Petrus does not teach or even suggest topically applying an effective amount of such a composition to a location proximal the carpal tunnel/median nerve as specified in the subject claim, let alone to do so to treat CTS/median nerve pressure.

In furtherance of the Applicants' assertion that the treatment of CTS/median nerve pressure by application of an NSAID formulation to an area proximal the carpal tunnel/median nerve is not taught or even suggested by Petrus, it is important to note that the only mention in Petrus of carpal tunnel syndrome at all is, as described above, a notation in the background section and there is no mention at all of treating median nerve pressure. Petrus does not describe the treatment of CTS or describe the application of an NSAID formulation to the area about the carpal tunnel/median nerve. NSAID compositions are mentioned in Petrus with reference to headaches, bursitis, controlling inflammation and discomfort following strabismus surgery, osteoarthritis, protection of osteoporosis, improved GI absorption, oral cancer, analgesia, anti-inflammatory and chondroprotective benefits, and gout symptoms. The specific references to particular application sites are eyes (eye drops to treat discomfort following strabismus surgery), joints (to provide analgesia, anti-inflammatory and chondroprotective benefits and to treat gout symptoms) and knees (to treat pain associated with osteoarthritis). There is no mention of applying the NSAID formulation specifically to an area proximal the carpal tunnel/median nerve, let alone such applications for the treatment of carpal tunnel syndrome/median nerve pressure.

The Examiner cites Biedermann et al. as "merely as a teaching reference to point out that diclofenac and indomethacin are known in the art as acetic acid derivatives". As such, Beidermann et al. do not teach or suggest the application of an NSAID formulation to treat CTS/median nerve pressure or applying an NSAID composition to an area proximal the carpal tunnel/median nerve to treat any condition, and thus fail to make up for the deficiencies of Petrus.

Accordingly, the references alone or in combination fail to teach or fairly suggest the topical application of an NSAID formulation to an area proximal the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure. As such, the references fail to teach or suggest all of the claimed limitations and thus a proper *prima facie* case cannot be made for at least this reason.

Furthermore, as the enclosed declaration of Dr. Larry Caldwell demonstrates, prior to the Applicants' work in this area, which includes the actual reduction to practice of the subject methods, one of skill in the art could not have had a reasonable expectation that topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure would be successful. Dr. Caldwell states that this lack of a reasonable expectation of success is based on the following premises: (1) it is well known in the art that just because an active agent is administered orally to treat a medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition; (2) it is well known in the art that just because an active agent is administered topically to treat one condition does not mean that it can be effective when topically administered to treat other conditions and Dr. Caldwell states that this is particularly true if the sites of topical application differ; and (3) because of the location of the target nerves which are responsible for carpal tunnel syndrome, it was not at all certain that the claimed methods would work prior to the actual reduction to practice reported in the application.

Accordingly, the Applicants submit that medical conditions cannot be adequately treated by simply changing the manner in which a formulation is applied as suggested by the Examiner. As such, a reasonable expectation of success cannot be expected by simply changing the manner in which the Petrus formulations are applied. Many formulations are known in the art that are efficient and/or effective at therapeutically relieving a medical condition by a particular method, but which are inefficient and/or ineffective when applied in a different manner such as a different

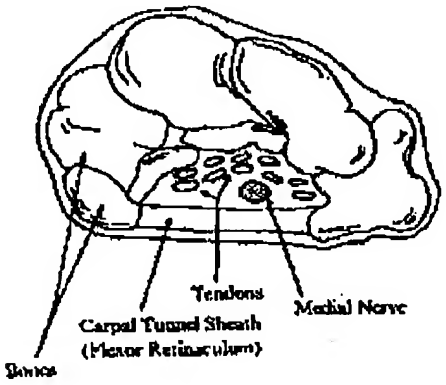
method. CTS/median nerve pressure is not exceptional in this respect. In fact, there are a variety of different causes of CTS/median nerve pressure thus further lowering the expectation of treatment success of treating CTS/median nerve pressure by changing the manner in which a formulation is applied to a subject. In fact, for a great number of patients, the cause of their carpal tunnel syndrome is unknown. Any condition that exerts pressure on the median nerve at the wrist can cause carpal tunnel syndrome. Some common conditions that can lead to carpal tunnel syndrome include obesity, pregnancy, premenstrual syndrome, menopause, renal failure, acromegaly, tuberculosis, fungal infection, high blood pressure, hypothyroidism, arthritis, diabetes, and injury or trauma. Tendon inflammation resulting from repetitive maneuvers, such as uninterrupted typing and the like, can also cause carpal tunnel symptoms. Some rare diseases can cause deposition of abnormal substances in and around the carpal tunnel, leading to nerve irritation. These diseases include amyloidosis, sarcoidosis, multiple myeloma, leukemia, and the like. There are also a number of different mechanisms by which drugs successfully treat such conditions and the experimental treatment of drugs for CTS/median nerve pressure has an extremely variable level of success, due in part to the varied different causes underlying CTS/median nerve pressure. Treatments for CTS/median nerve pressure are largely empirically determined, and typically a low expectation of success may be predicted for a particular composition and method of treatment for CTS/median nerve pressure due at least in part to the various causes.

As noted by Dr. Caldwell, just because an agent is administered by a particular route such as the oral route does not mean that is can be effective when administered via another route such as a transdermal route. Accordingly, while NSAID's have been administered orally to treat certain conditions, a reasonable expectation of success cannot be predicted when an NSAID is administered topically to treat the same or different condition.

Furthermore, even if the routes of administration are the same, e.g., topical routes, a reasonable expectation of success cannot be expected if the conditions treated differ. As Dr. Caldwell notes, this is particularly true if the sites of topical administration also differ. Accordingly, a reasonable expectation of success cannot be expected by modifying the invention of Petrus to change not only the site of topical application, as Petrus does not describe topically applying a formulation to the area of the carpal tunnel/median nerve, but to also change the conditions being treated, as Petrus does not specifically describe the treatment of carpal tunnel

syndrome/median nerve pressure.

Still further, as explained by Dr. Caldwell, a reasonable expectation of success could not be expected prior to the actual reduction to practice by the Applicants because of the location of the target site (carpal tunnel nerves). In the subject methods, the NSAID component must cross a barrier to be effective as barriers are present in the area of the carpal tunnel/median nerve. The carpal tunnel is the interior of the wrist through which the medial nerve, tendons and blood vessels pass. Three sides of the carpal tunnel are bone and the other side is a thickened sheath, the flexor retinaculum, which is made of ligament material. The figure provided below shows the bone and sheath barriers that surround the median nerve on all sides.



The same expectation of success cannot be predicted from the application of a particular therapeutic agent to an area that does not include such barriers such as bone barriers, ligament barriers, and the like, to treat a given condition. In other words, a reasonable expectation of success for treating a condition cannot be predicted by simply changing the application site of a formulation from a site that does not include barriers such as bone barriers, ligament barriers, and the like, to a site that does include such barriers. As Dr. Caldwell states in the attached declaration, prior to the Applicants' work in this area, it was not at all certain that topically administering an NSAID formulation to an area about the carpal tunnel/median nerve would effectively treat CTS/median nerve pressure at least in part because it was not certain that a therapeutically effective amount of NSAID would cross a barrier to reach the target site.

As also noted by Dr. Caldwell, further adding to this low expectation of success is the fact that carpal tunnel syndrome originates deep within the nerves of the wrist and thus the active

agent must penetrate deeply in order to reach the target site. Prior to the Applicants' work in the area, it was not at all certain that a sufficient amount of the active agent would penetrate deeply enough to be effective at treating CTS/median nerve pressure.

The expectation of success is further lowered when not only is the application site different, but the condition being treated is also different. As Dr, Caldwell states in the attached declaration, it is known in the art that just because a topically administered agent is effective at treating one condition does not mean it can be effective at treating when topically administered to treat other conditions, especially if the administration sites differ. Accordingly, a reasonable expectation of success of topically applying an agent to an application site "X" to treat condition "Y" cannot be predicted from the topical application of an agent to an application site "A" to treat condition "B". For example, even if a therapeutic agent is effective at treating a particular type of malady such as a particular type of musculoskeletal disorder by the topical application to a particular area of the body, there is no reasonable expectation of success that the topical application of the same therapeutic agent will be effective at treating different types of musculoskeletal disorders when applied to the same area of the body, let alone effective at treating different types of maladies when topically applied to a different area of the body. While Petrus describes the application of an NSAID formulation to treat certain conditions but does not specifically describe the treatment of carpal tunnel syndrome by topical application of an NSAID formulation, there is no reasonable expectation of success, and in fact a low expectation of success may be predicted, from the application of an NSAID formulation to an area other than that described in Petrus to treat a condition other than that described in Petrus.

Although the combination of references suggested by the Examiner may suggest that it would be *obvious to try* applying an NSAID formulation to an area proximal to the carpal tunnel/median nerve to treat CTS/median nerve pressure, there is certainly no prediction that the treatment would be successful, especially in view of the barriers that surround the area, the requirement of deep penetration of the active agent, and the like. A reasonable expectation of success is not taught in the cited references as neither of the references teaches the successful application of a topical NSAID formulation to an area about the carpal tunnel/median nerve to treat any condition, let alone to treat CTS/median nerve pressure. In fact, as noted above, the only examples of actual use of a NSAID formulation are Example 1 which describes the use of a gel to provide analgesia, anti-inflammatory and chondroprotective benefits when applied to

joints and does not describe the application of an NSAID formulation to an area about the carpal tunnel/median nerve to treat CTS/median nerve pressure; Example 2 which describes application of a gel to painful joints for gout symptoms and does not describe the application of the gel to an area about the carpal tunnel/median nerve to treat CTS/median nerve pressure; Example 3 which merely describes a gel for analgesia, anti-inflammatory relief, protection from osteoporosis and chondroprotective advantages and does not describe the application of the gel to an area about the carpal tunnel/median nerve to treat CTS/median nerve pressure; and Example 4 which is specifically directed to using the gel of Example 3 on the knee to treat knee pain associated with osteoarthritis of the knee and does not describe the application of the gel to an area about the carpal tunnel/median nerve to treat CTS/median nerve pressure.

However, the Applicants have reduced the claimed invention to practice- the results of which are reported in the experimental section of the application and which demonstrate the successful treatment of carpal tunnel syndrome by topically applying a topical NSAID formulation to a subject. Specifically, the experimental section of the present application describes the application of NSAID-containing patches to the plantar aspect of each wrist to successfully treat carpal tunnel syndromes. The experimental section reports the unexpected result that after a subject wore NSAID-containing patches applied to the plantar aspect of each wrist overnight, all carpal tunnel symptoms were absent the next morning. Furthermore, unexpectedly the symptoms remained absent for three weeks following the patch application and after three weeks the symptoms were again relieved after overnight treatment with an NSAID-containing patch. Accordingly, while the cited references do not provide any reasonable expectation of success of treating CTS/median nerve pressure by application of an NSAID-containing formulation to an area about the carpal tunnel/median nerve, the Applicants have shown unexpected results of such a treatment.

Furthermore, with respect to Claims 24-28, the Examiner asserts that there is no patentable distinction between applying a cream or film to a patient and using a wristband that includes a patch. Claims 24 and 28, and the claims that depend therefrom, have been amended to specify that the patch is a hydrogel patch. Neither of the cited references teaches the application of a wrist band that includes an NSAID formulation-containing hydrogel patch to an area about the carpal tunnel/median nerve to treat CTS/median nerve pressure. A patch and particularly a hydrogel patch is not analogous to a film. Hydrogels may be broadly characterized as aqueous

compositions capable of absorbing water and maintaining a gel-like state. Due to the water content of hydrogel patch compositions, they are tolerated by the skin so that they may remain in contact with skin for longer periods of time as compared to, e.g., films and the like.

Furthermore, the Applicants submit that a wrist band that includes a patch in the subject methods provides significant advantages relating to the efficiency and effectiveness of the active agent. The patch facilitates the delivery or administration of the NSAID component into the skin. The patch enhances or increases the penetration of the NSAID component into the skin. The wrist band ensures that the patch remains secured in position about the carpal tunnel/median nerve. Accordingly, the wrist band/patch as claimed is patentably distinct from creams, etc. for at least the reason that a distinct advantage is provided by the use thereof and neither of the references teaches or even suggests a patch of any kind, let alone a hydrogel patch as claimed in these claims.

For at least the reasons described above, the Applicants respectfully request that this rejection be withdrawn.

Claims 1-18 and 24-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Petrus (U.S. 6,399,093 B1) in view of Edwards (U.S. Patent No. 5,989,559) and Biedermann et al. The Applicants respectfully submit that Claims 1-18 and 24-28 are patentable over the cited references.

As describe above, a *prima facie* case of obviousness cannot be made in view of Petrus and Biedermann et al. as these references fail to teach or suggest topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat a subject for CTS/median nerve pressure. Furthermore, a reasonable expectation of success of topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat a subject for CTS/median nerve pressure cannot be predicted from the teachings of these two references. These deficiencies are not overcome by Edwards as Edwards fails to teach or suggest topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel or provide any indication that a reasonable expectation of success would be predicted from such a method because Edwards is solely directed to a banana peel extract composition.

The Examiner states that Edwards is used to show that it is "commonly known in the prior art to apply topical medication on or near the loci of the sites of pain, such as those caused by carpal tunnel syndrome". However, the specific teachings of Edwards of applying a banana peel extract to particular areas of a subject do not support the broad conclusion stated by the Examiner. Just because one agent is administered topically to a site to treat one condition, does not mean that a reasonable expectation of success can be predicted by topically administering another agent to treat the same or other condition.

Edward's teachings of applying a banana peel extract to legs to treat sore muscles (Example L), applying a banana peel extract to treat an insect bite (Example N), applying a banana peel extract to a toe, knee, hip and lumbro-sacral joints to treat pain (Example O), applying a banana peel extract to a wrist to treat swelling and pain from carpal tunnel syndrome (Example P), and applying a banana peel extract to an ankle to treat arthritic pain do not provide a reasonable expectation of success for applying a topical NSAID formulation to an area about the carpal tunnel/median nerve to treat CTS/median nerve pressure as Edwards does not mention an NSAID formulation at all.

Furthermore, with respect to Claim 24-28, the cited references fail to teach or suggest the application of a wrist band that includes an NSAID formulation-containing hydrogel patch to an area about the carpal tunnel/median nerve to treat CTS/median nerve pressure. As described above, the use of a wrist band that includes a patch provides significant advantages relating to the efficiency and effectiveness of the active agent.

For at least the reasons described above, the Applicants respectfully request that this rejection be withdrawn.

Claims 19-23 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Petrus in view of Biedermann et al., and Shudo et al. The Applicants respectfully submit that Claims 19-23 are patentable over the cited references

Claim 19, and the claims that depend therefrom, specify instructions for using an NSAID in the practice of a method according to Claim 1. As described above, the cited references either alone or in combination fail to teach or suggest a method according to Claim 1 and prior to the Applicants' work described in the present application, one of skill in the art could not have had a

reasonable expectation of success in a method of topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure. Accordingly, the cited references fail to teach or suggest instructions for practicing the method of Claim 1, as claimed in the subject claims.

For at least the reasons described above, the Applicants respectfully request that this rejection be withdrawn.

Claims 19-23 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Petrus in view of Edwards, Biedermann et al., and Shudo et al. The Applicants respectfully submit that Claims 19-23 are patentable over the cited references.

For reasons analogous to those described above, i.e., (1) neither Petrus, Edwards, Biedermann et al., or Shudo et al. teach or suggest a method according to Claim 1 and (2) prior to the Applicants' work described in the present application, one of skill in the art could not have had a reasonable expectation of success in a method of topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure, these references fail to teach or suggest instructions for practicing the method of Claim 1, as claimed in the subject claims.

For at least the reasons described above, the Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

If, in the opinion of the Examiner, a telephonic interview would expedite prosecution of this application, the Examiner is invited to contact the undersigned at (650) 833-7770.

If the Patent Office determines that fees, including extensions of time, are required, the Applicants hereby petition for any required relief, including extensions of time, and authorize the Commissioner to charge the cost of such to our Deposit Account No. 50-0815, Order No. CALD005.

Respectfully Submitted,

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